REMARKS

Claims 25-62 are pending in the instant application, and claims 1-24 have been previously cancelled. Claims 55-62 have been withdrawn from consideration by the Examiner as directed to non-elected subject matter. Thus, claims 25-54 have been examined according to the Office Action. The Office Action has asserted at least one of the following four rejections against claims 25-54: non-statutory obviousness-type double patenting, indefiniteness, lack of enablement, and/or unpatentable under 35 U.S.C. § 103.

Provisional Non-Statutory Double Patenting Rejection

Claims 25-28 have been rejected on the ground of provisional non-statutory obviousness-type double patenting as purportedly being unpatentable over claims 20-24 in co-pending U.S Patent Application No. 10/532,320 ("the '320 Application"). As of the date of this Amendment, claims 20-24 in the '320 Application have not been allowed. As such, Applicants are not required to address this provisional rejection at this time, and will address this provisional rejection if and when claims 20-24 in the '320 are allowed.

Rejection under 35 U.S.C. § 112, Second Paragraph

Claim 44 has been rejected under 35 U.S.C § 112, second paragraph, as being indefinite for its recitation of "an effective amount." Applicants respectfully traverse this rejection because a person of ordinary skill in the art would understand the meaning of "an effective amount." Such a person would know standard analytical techniques to determine the amount of a particular aromatase inhibitor needed to suppress blood serum 17β-estradiol levels to below 10 pg/ml in a subject. The standard analytical techniques do not constitute undue experimentation to carry out a dosage-effect study for establishing the minimum dosage of aromatase inhibitor that is required to reduce blood serum 17β-estradiol levels to below 10 pg/ml. For these reasons, a skilled artisan would understand the meaning of "an effective amount." Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

On pages 4 and 5, the Office Action contends that undue experimentation is necessary to practice the recited invention with "an effective amount" of each and every aromatase inhibitor, and therefore claim 44 is indefinite. According to MPEP § 2171, the issue with regard to 35 U.S.C.

§ 112, second paragraph, is whether the scope of the claim is clear to a hypothetical person possessing the ordinary level of skill in the pertinent art. "The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent."[1]

By reading claim 44, the public would be informed that "an effective amount" is an amount that would suppress blood serum 17β-estradiol levels to below 10 pg/ml in a subject. The correct analysis under 35 U.S.C. § 112, second paragraph, is not whether undue experimentation (which Applicants contend is not required to practice claim 44), but whether the claim delineates the boundaries of the patent. Claim 44 clearly delineates the boundaries to include any amount of aromatase inhibitor that would suppress blood serum 17β-estradiol levels to below 10 pg/ml in a subject. Accordingly, reconsideration and withdrawal of this rejection is respectfully requestsed.

Rejection under 35 U.S.C. § 112, First Paragraph

Claims 25-44 have been rejected under 35 U.S.C. § 112, first paragraph, as not enabling a person of ordinary skill in the art to make or use the claimed invention. Particularly, the Office Action contends that the Specification does not enable such a person to prophylactically treat an estrogen-sensitive tumour and does not enable a skilled artisan to co-administer an effective amount of aromatase inhibitor.

When asserting an enablement rejection, the Patent Office bears the burden of setting forth a reasonable explanation as to why it believes that the claims are not enabled by the specification. *In re Wright*, 999 F.2d 1557, 1561-1562 (Fed. Cir. 1993); *In re Stoughton*, No. 2005-2235, App. No. 09/038,894, 2006 WL 1665412 at *4 (BPAI 2006). Precise predictability is not the standard to employ. *In re Corpet*, No. 2004-1790, App. No. 09/836,971, 2004 WL 2733634 (BPAI 2004).

[1] MPEP § 2173.

In *Corpet*, the examiner rejected claim 12 as not enabled by the specification. 2004 WL 2733634 at *1. Claim 12 recited "[a] method of preventing colon or rectum cancer comprising administering to a mammal a therapeutically effective amount of a non-fermented osmotic polyol laxative." *Id.* The rationale for rejecting claim 12 was based on the argument

> that the recitation of preventing "extend[s] the treatment to those patients in which rectal and colon cancers may occur at any point of time in [the] future." [Citation omitted.] With respect to the state of the art, the examiner apparently recognizes that "[t]he state of the art recognizes that increased intake of dietary fibers contribute to the increased bowel movements and thus result in lowering the risk of colon cancers," but asserts that "the art does not teach or recognize a complete prevention of the above claimed cancers." [Citation omitted.] Finally, with respect to guidance of the specification and examples, the examiner focuses on the lack of teaching of an understanding of when the cancer may occur.

Id. The Board determined that the examiner's rationale required "precise predictability as to the time when the colon or rectal cancer will appear, and also appears to require 100% prevention. That is not, however, a requirement under 35 U.S.C. § 112, first paragraph." *Id.* at *2. Due to this flawed rationale, the Board held that the examiner failed to meet his burden and reversed the rejection. *Id.* at *3.

The Board reversed a similar rejection in *In re Goldenberg*, App No. 08/183,381, 2002 WL 31105508 (BPAI 2002). In *Goldenberg*, the examiner argued that "'[a]pplicant broadly claims an anti-idiotype vaccine to prevent cancer, AIDS and malaria, but the specification fails to enable the vaccine(s) and effectively teach how to make and/or use said vaccines to achieve this.'" *Id.* at *3. The Board held that this "failed to provide the evidence necessary to demonstrate that appellants' disclosure does not enable their claimed invention. While some of the claimed combinations may be inoperative, the examiner failed to establish that the number of inoperative combinations is so significant, that one of ordinary skill in the art would have to experiment unduly in order to practice the claimed invention." *Id.* at *4. Like *Corpet*, the Board in *Goldenberg* reversed the rejection because the examiner required 100% predictability, which is not the standard for enablement.

The rejection of claims 25-44 with regard to the recitation of "prophylactycally treating" is similar to the rejections asserted in *Corpet* and *Goldenberg*. On page 15, the Office

Action contends that "one of ordinary skill in the art would be required to conduct an undue amount of experimentation to reasonably and ***accurately determine*** whether said estrogenic compound when co-administered with an aromatase inhibitor in corresponding instant method does in fact effectively and prophylactically treat the occurrence of said estrogenic-sensitive tumors." This rationale suggests that the Patent Office is requiring the Applicants to show precise predictability, which the above-discussed cases clearly demonstrate is improper. Therefore, a *prima facie* case that the recites claims are not enabled with respect to prophylactically treating estrogen-sensitive tumors has not been established.

The Office Action also contends that the Specification fails to enable a skilled artisan to make and use an effective amount of aromatase inhibitor as recited in claim 44 (Office Action of pages 10-15). On page 15, the Office Action contends that "one of ordinary skill in the art would be required to conduct an undue amount of experimentation to predict whether the amount of 0.05 mg or other amount of anastrozole is capable of suppressing blood serum 17β-estradiol level to below 10 pg/ml." To the contrary, a person of ordinary skill in the art would only have to conduct routine experiments to determine the effective amount of the aromatase inhibitor that reduces blood serum 17β-estradiol levels to below 10 pg/ml.

This rejection is similar to the one in *Ex parte Brenner*, Appeal No. 98-1012, App. No. 08/117,342, 1999 WL 33205253 (BPAI Mar. 23, 1999). In *Brenner*, the examiner argued that claim 5 was not enabled by the specification because it did "not recite the concentration at which Cefsulodin suppresses non-coliform bacteria but not coliform bacteria." *Brenner*, 1999 WL 33205253 at *3. The Board reversed this rejection because "[w]hile it may take considerable experimentation, it is simply a matter of mixing certain agents in a buffered vehicle, with the necessary chromogen and fluorogen detectors, until an E coli/coliform detecting medium is obtained that can both encourage coliform growth and suppress Gram-positive and non-coliform bacteria." *Id.* at *4.

Likewise, in this case, it is a simple matter of mixing the estrogenic component with increasing quantities of aromatase inhibitor until the goal, reducing blood serum 17β-estradiol levels to below 10 pg/ml, is reached. Measuring serum estradiol levels is common practice in the art.

Wikipedia discusses serum estradiol measurements as a useful technique for detecting basline estrogen in women with amenorrhra or menstrual dysfunction, and for detecting hypoestrogenicity, and menopause.[2] This information establishes that serum estradiol measurements are routine analytical tools used in the field of endocrinology. Therefore, claim 44 is enabled because only routine experimentation is required to determine the appropriate amount of the aromatase inhibitor.

For these reasons, Applicants respectfully request that this rejection be reconsidered and withdrawn.

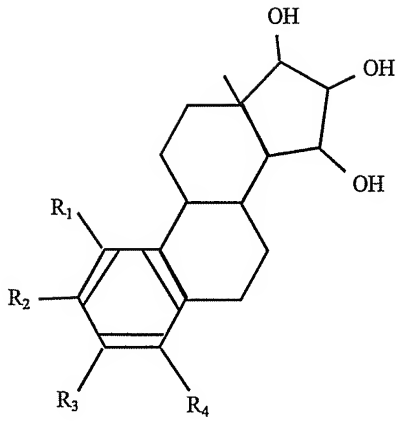
Rejection under 35 U.S.C. § 103

Claims 25-28, 30-38, 40-48 and 50-54 have been rejected under 35 U.S.C. § 103 as purportedly being unpatentable over Elliesen (U.S. Patent Application No. 2002/0156059) in view of Holinka *et al.* (Biology of Reproduction, 1980, 22, 913-926) ("Holinka (1980)"). Applicants respectfully traverse this rejection because prior to the filing of the instant application a skilled artisan would not reasonably expect that administering the recited formulas, for example, estetrol would be capable of treating or prophylactically treating estrogen-sensitive tumors, or, as recited in claims 31, 41 and 51, that the recited estrogenic components would be effective when orally administered.

The claimed invention

Claim 25 is directed to a method of treating or prophylactically treating estrogen-sensitive tumors in a mammal. The method comprises administering a therapeutically effective amount of an estrogenic component selected from the group consisting of substances represented by the following formula:

[2] http://en.wikipedia.org/wiki/Estradiol



in which formula R_1, R_2, R_3, R_4 independently are a hydrogen atom, a hydroxyl group or an alkoxy group with 1-5 carbon atoms; precursors capable of liberating a substance according to the aforementioned formula which precursors are derivatives of the present estrogen substances, wherein the hydrogen atom of at least one of the hydroxyl groups has been substituted by an acyl radical of a hydrocarbon carboxylic, sulfonic acid or sulfamic acid of 1-25 carbon atoms; tetrahydrofuranyl; tetrahydropyranyl; or a straight or branched chain glycosydic residue containing 1-20 glycosidic units per residue; and mixtures of one or more of the aforementioned substances and/or precursors. One example of the recited estrogenic component is estetrol. Claims 26-54 ultimately depend from claim 25.

The cited references

On pages 16-17, the August 17, 2008 Office Action acknowledged that "Elliesen, J. does not expressly teach the structure of an estrogenic compound, which contains up to four hydroxyl groups, such as estetrol," but contended that it would have been obvious to a skilled artisan at the time of the invention to combine Elliesen's use of an oral form of estrogen and aromatase inhibitor with Holinka (1980)'s purported teaching that estetrol has comparable estrogenic effect as other natural estrogens because estetrol is capable of stimulating uterine, and therefore, a skilled artisan would reasonably expect to successfully treat and reduce the risk of breast cancer because estetrol and estriol are structurally similar estrogens and have similar estrogenic properties. Applicants respectfully disagree with this contention because one would not reasonably expect to successfully treat or prophylactically treat estrogen-sensitive tumors in view of Elliesen and Holinka (1980) because Holinka (1980) does not teach a method of treating or prophylactically treating estrogen-sensitive tumors, nor do they overcome the believe that, prior to the disclosure of the instant invention, estetrol was considered not to be pharmacologically active. In fact, Holinka (1980)

teaches that the estrogenic potency of estetrol is very low relative to estradiol and estriol.

On page 15, the August 17, 2008 Office Action alleged that "Elliesen, J. also teaches that natural estrogens that have a longer action, such as estriol ... are particularly suitable (¶ 0020)." However, Elliesen ¶ 20 has no bearing on the claimed formulas and does not suggest, as contended in the Office Action, that natural estrogens, such as estriol, have a longer action. The first sentence of Elliesen ¶ 20 reads as follows: "As natural estrogens, these are in particular estradiol as well as its esters that have a longer action, such as valerate, etc., or estriol." Clearly, since estriol is not an ester of estradiol, the reference to longer action does not relate to estriol. While esters of estradiol have prolonged estrogenic activity, estriol is known as a very short-acting estrogen.

Holinka (1980) is directed to a study comparing the effects of estetrol and tamoxifen against estriol and estradiol on immature rat uteri. In the study, rats were injected with estetrol and tamoxifen subcutaneously, each day, at a dose of 50 μg per 100 g of bodyweight. Estradiol and estriol was administered at a dose of 1 μg per 100 g bodyweight. The authors concluded that "on the basis of the present biochemical and morphological results, it is concluded that estetrol ('E_4') and tamoxifen have estrogenic effects on immature rat uteri. However, ***the estrogenic potency of E_4 relative to E_2 or E_3 was low at the dosage and timing of administration used in these experiments ....These results suggest that the conversation of E_2 to E_4 in the human fetus might represent an efficient mechanism of inactivation of the placental hormone.***[3]

The cited references are inoperable to enable one of ordinary skill to use estetrol

The portions of Holinka (1980) cited above show that estetrol do not have comparable estrogenic effect as other natural estrogens, for example, estriol. The mere fact that estetrol is capable of stimulating uterine growth does not mean that estetrol has comparable estrogenic activity as natural estrogens such as estradiol and estriol. As Holinka (1980) states, the estrogenic potency of estetrol (E_4) is low compared to that of estradiol (E_2) or estriol (E_3). Therefore, after considering the cited references, one would not have a reasonable expectation of successfully combining the method described in Elliesen with the teachings in Holinka (1980) because Holinka (1980) fails to teach or provide any reason for a skilled artisan to employ estetrol instead of estriol since estetrol is described

as having a low estrogenic activity as compared to estriol.

The conclusion stated in Holinka (1980) – that estetrol has lower estrogenic activity as compared to estriol or estradiol – is in-line with observations made in other scientific literature. References enclosed with the Information Disclose Statement of November 19, 2007 further evidence this:

- Levine *et al.*, 1984, "Uterine vascular effects of estetrol in non-pregnant ewes," AM. J. OBSTET. GYNECOL., 148:73, 735-738: "When intravenously administered in non-pregnant ewes, estetrol is 15 to 30 times less potent than estriol and 17.beta.-estradiol in uterine vasodilation;"
- Jozan *et al.*, 1981, "Different effects of oestradiol, oestriol, oestetrol and of oestrone on human breast cancer cells (MCF-7) in long term tissue culture," ACTA ENDOCRINOLOGICA, 98, 73-80: "Estetrol agonistic potency is 2% of the magnitude observed for 17.beta.-estradiol in in-vitro cell proliferation;"
- Holinka *et al.*, 1980, "Comparison of effects of estetrol and tamoxifen with those of estriol and estradiol on the immature rat uterus," BIOL. REPROD. 22, 913-926: "Subcutaneously administered estetrol has very weak uterotrophic activity and is considerable less potent than 17(3-estradiol and estriol;"[4]
- Holinka *et al.*, 1979, "In vivo effects of estetrol on the immature rat uterus," BIOL. REPROD. 20, 242-246: "Subcutaneously administered estetrol has very weak uterotrophic activity and is considerable less potent than 17.beta.-estradiol and estriol;"
- Tseng *et al.*, 1978, "Heterogeneity of saturable estradiol binding sites in nuclei of human endometrium Estetrol studies," J. STEROID BIOCHEM. 9, 1145-1148: "Relative binding of estetrol to estrogen receptors in the human endometrium is 1.5% of 17.beta.-estradiol;"

[3] Emphasis added; Holinka (1980) at abstract.
[4] Holinka (1980) was not disclosed in the IDS of November 19, 2007; however, it was cited by the Patent Office.

- Martucci *et al.*, 1977, "Direction of estradiol metabolism as a control of its hormonal action-uterotrophic activity of estradiol metabolites," ENDOCRIN. 101, 1709-1715: "Continuous administration of estetrol from a subcutaneous depot shows very weak uterotrophic activity and is considerably less potent than 17.beta.-estradiol and estriol;"
- Tseng *et al.*, 1976, "Competition of estetrol and ethynylestradiol with estradiol for nuclear binding in human endometrium," J. STEROID BIOCHEM. 7, 817-822: "The relative binding constant of estetrol binding to the estrogen receptor in the human endometrium is 6.25% compared to 17.beta.-estradiol (100%);" and
- Martucci *et al.*, 1976, "Uterine estrogen receptor binding of catecholestrogens and of estetrol (1,3,5(10)-estratriene-3,15α, 16α - a, 17β-tetrol)," STEROIDS, 27, 325-333: "Relative binding affinity of estetrol to rat uterine cytosol estrogen receptor is 0.5% of 17β-estradiol (100%). Furthermore, the relative binding affinity of estetrol to rat uterine nuclear estrogen receptor is 0.3% of 17β-estradiol (100%)."

In sum, these references related to investigation of estrogenic potency of estetrol and conclude that estetrol is a very weak estrogen. Moreover, Applicants are unaware of any recorded pharmaceutical use of estetrol up until the present invention.

Therefore, an artisan of ordinary skill in the field of steroids would not conclude from Holinka (1980) that estriol and estetrol can be used interchangeably, and therefore would not choose estetrol for use in the estrogen replacement method as described in Elliesen. Additionally, Elliesen viewed in combination with Holinka (1980) does not teach a method of treating or prophylactically treating estrogen-sensitive tumors.

A person of ordinary skill would not have reasonably expected that estetrol could be successfully used to treat or prophylactically treat estrogen-sensitive tumors.

Prior to the disclosure of the present invention, estetrol was not believed to be a potent natural estrogen.[5] In fact, one of ordinary skill believed that estetrol would not have any pharmacological effect due to its low estrogenic potency, and the fact that estradiol and estriol had

[5] See Specification at ¶¶ 12 to 21; see also Holinka (1980), abstract.

such short terminal elimination half-lifes. To further evidence these points, Applicants submit declarations from third-party artisans in the field, and a declaration from one of the co-inventors.

As these declarations establish, prior to the disclosure of this invention, one of ordinary skill in the art believed that estetrol would not have been pharmacologically active.[6] This is because it was known in the art that estetrol had a considerably lower estrogen receptor affinity than estradiol or estriol.[7] Specifically, one of ordinary skill would have expected estetrol to be less effective than estradiol or estriol because the Holinka articles suggest that estetrol is a much weaker estrogen than the already weak estrogen estriol, given that estetrol injected subcutaneous at 50 μg/100 g body mass exhibited less estrogenic activity than estriol injected subcutaneous at 1 μg/100 g body mass.[8] Estriol is a very weak estrogen due to its low receptor affinity in combination with its very short half-life of 5-10 minutes.[9] Since the Holinka articles teach that estrogenic activity of estetrol is at least 50 times lower than that of a weak estrogen for which very few practical applications exists, the Holinka articles would not have provided a motivation for a person of ordinary skill in the art to investigate the potential pharmacological usefulness of estetrol.[10] Instead, these articles teach away from estetrol having any pharmacological effect.

Thus, the recited invention is patentable over the cited references because one of ordinary skill in the art would not reasonably expect that he or she could successfully use estetrol for treating or prophylactically treating estrogen-sensitive tumors. When making a rejection under 35 U.S.C. § 103, the examiner has the burden of establishing a *prima facie* case of obviousness. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). As part of a *prima facie* case, an examiner must establish some reason to combine the references. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 131 (2007); *Takeda Chemical Industries, Ltd. v. Alpharpharm Pty., Ltd.*, 492 F.3d 1350, 1356-1357 (Fed. Cir. 2007). The *KSR* Court acknowledged the importance identifying a reason that would have

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[6] See Declaration by Strauss at ¶¶ 8-9; see also Declaration by Speroff at ¶¶ 8-9; see also Declaration by Coelingh Bennink at ¶¶ 3 and 5.

[7] See Holinka (1980), abstract, see also Declaration by Strauss at ¶¶ 15-16, 18 and 20; see also Declaration by Speroff at ¶¶ 15-16, 18 and 20; see also Declaration by Coelingh Bennink at ¶¶ 3 and 5.

[8] Declaration by Strauss at ¶ 16; Declaration by Speroff at ¶ 16; Declaration by Coelingh Bennink at ¶¶ 5.

[9] Declaration by Strauss at ¶ 16; Declaration by Speroff at ¶ 16; Declaration by Coelingh Bennink at ¶¶ 5.

[10] Declaration by Strauss at ¶¶ 15-16; and Declaration by Speroff at ¶¶ 15-16.

prompted a person of ordinary skill in the art to combine the elements in the way the claimed invention does. *KSR Int'l*, 127 S.Ct. at 1731; *Takeda Chemical*, 492 F.3d at 1356-1357. Repeatedly throughout the *KSR* decision, the Court discussed the importance that the result obtained by a particular combination was predictable to one of ordinary skill in the art. *KSR Int'l*, 127 S.Ct. at 1731 and 1739-1742.

A combination of known elements will not yield predictable results if the references teach away from the claimed invention. *Takeda Chemical*, 492 F.3d at 1359; *Ortho-McNeil Pharmaceutical, Inc. v. Mylan*, 520 F.3d 1358, 1364 (Fed. Cir. 2008); and *Ex parte Ikeda*, App. No. 08/352,079, Appeal 2008-0492, Slip Op. at 7 (BPAI Mar. 26, 2008). For example, in *Takeda Chemical*, the post-*KSR* Federal Circuit noted that the recited compound, which was a modified version of compound b, was not recognized at the pertinent time as a suitable candidate for treatment of Type II diabetes. 492 F.3d at 1359. *Takeda Chemical* involved United States Patent No. 4,687,777, which was directed to a compound for the treatment of Type II diabetes. *Id.* at 1352-1354. The defendant argued that the patent was obvious in view of a reference that disclosed compound b, because the claimed compound could be synthesized from compound b by routine means. *Id.* at 1357. However, the Federal Circuit affirmed that the patent was not obvious because the prior art taught away from choosing compound b as a starting point. *Id.* at 1359-1361. Compound b was known to have unwanted side effects, and there was nothing in the prior art to suggest that homologation would decrease the unwanted side effects. *Id.* at 1359-1360.

In a more recent case, the Board reversed an examiner's rejection for failing to provide the requisite reason to combine the references. *Ikeda*, App No. 08/352,079 at 7. The *Ikeda* application was directed to a method of removing hydrocarbons from exhaust gases. *Id.* at 2. In pertinent part, the claims recited an absorption catalyst B located downstream of a catalyst A in the direction of the exhaust gas. The claims were rejected as unpatentable under 35 U.S.C. § 103 in view of Swaroop, Abe and Patil. *Id.* at 3. Swaroop taught positioning the absorption catalyst B upstream catalyst A. *Id.* at 5. To remedy the deficiency in the art, the examiner cited "Patil and Abe as evidence of the 'coventionality of positioning the adsorbent catalyst 1 either upstream or downstream of a [three-way] catalyst 3' and thus conclude[d] that it would have been obvious to one of ordinary skill in this art to select an appropriate location for the adsorbent catalyst 16 in the

apparatus of Swaroop ...." *Id.* at 5-6. The Board held that

> The Examiner has failed to provide any cogent reason or technical discussion to support the conclusion that one of ordinary skill in this art would have employed the relative positions of the catalysts in Abe and Patil without the use of the other teachings of these references, namely an auxiliary heater and bypass lines with valving. Second, the Examiner has not explained why one of ordinary skill in this art would have used the teachings of Patil, requiring bypass lines and valving, when Swaroop specifically ***teaches away*** from the use of valving and bypass lines [*citation omitted*]. Third, the Examiner has not supplied convincing reasoning or technical discussion to support the proposed switch in relative position of the catalysts when Swaroop specifically teaches that the exhaust gas is "modified" by the adsorbent catalyst and this modified form of the exhaust gas is *then* sent to the main or three-way catalyst to undergo conversion to innocuous products [*citation omitted*]. ... Fourth, the Examiner has not explained why one of ordinary skill in this art would have ***proceeded contrary to the teachings of Patil***, namely the teachings that "it is not possible merely to place zeolite 'in-line' in the exhaust system with the [main] catalyst has reached an effective temperature and unconverted hydrocarbons would still be discharged to the atmosphere" [*citation omitted*].

Emphasis added, *Ikeda*, App. No. 08/352,079 at 7.

Following the reasoning stated in *Takeda Chemical* and *Ikeda*, the Office Action must provide some explanation why one of ordinary skill in the art would believe that estestrol would be pharmacologically active when estetrol was believed to be too weak an estrogen to be useful. As discussed above, prior to the publication of this invention, one of ordinary skill in the art would not have expected estetrol to be pharmacologically active because it was known that estetrol was a weaker estrogen than the already weak estrogen estriol.

It was not until the Applicants discovered estetrol's unexpectedly long terminal elimination half-life that it became apparent that estetrol could be pharmacologically useful. Prior to the disclosure of this invention, there was no publicly available data about the terminal elimination half-life of estetrol, about estetrol's binding to SHBG or about estetrol's effect on SHBG production.[11] Since, estradiol and estriol have terminal elimination half-lifes of about 30 minutes and 5-10 minutes respectively, it was believed that estetrol, another natural estrogen, would likewise have a short, if not shorter, terminal elimination half-life.[12] Unexpectedly, the Applicants discovered that estetrol has a terminal elimination half-life of about 28 hours.[13]

> A person of ordinary skill in the art would have expected estetrol to be more comparable to estriol than estradiol given that (i) estetrol differs from estriol by only 1 hydroxy group and from estradiol by 2 hydroxy groups and (ii) both estriol and estetrol are produced during pregnancy. Hence, Applicants' finding that estetrol has a terminal elimination half-life that is 168-336 higher than that of the other pregnancy hormone estriol, was very unexpected and provided the clue towards its pharmacological usefulness.[14]

Like *Takeda Chemical*, one of ordinary skill in the art would have had no reason to use estetrol because it was believed not to be pharmacologically active. Maintaining a rejection based on the premise that it was known in the art that estetrol can be used instead of estriol is improper for the same reasons that the rejection in *Ikeda* was improper – because the prior art teaches away from using estetrol. Thus, as part of a *prima facie* case of obviousness, there must be some explanation why one of ordinary skill in the art would consider using estetrol when the prior art teaches that it is not pharmacologically active. Since such an explanation has not been provided, a *prima facie* case of obviousness has not been established. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

It was unexpected to discover that estetrol was pharmacologically active

Additionally, the unexpected result that estetrol is pharmacologically active rebuts the

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[11] Declaration by Coelingh Bennink at ¶¶ 4.

[12] Declaration by Strauss at ¶ 17; and Declaration by Speroff at ¶ 17.

[13] Declaration by Strauss at ¶ 17; and Declaration by Speroff at ¶ 17.

[14] Declaration by Strauss at ¶ 17; and Declaration by Speroff at ¶ 17.

obviousness rejection. *Ormco Corp. v. Align Technology, Inc.*, 463 F.3d 1299, 1311, 79 U.S.P.Q.2d 1931 (Fed. Cir. 2006); MPEP § 2145; *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). To establish unexpected results, the Applicant must "establish (1) that there actually is a difference between the results obtained through the claimed invention and those of the prior art, *In re Klosak*, 455 F.2d 1077, 59 CCPA 862 (1972); and (2) that the difference actually obtained would not have been expected by one skilled in the art at the time of invention, *Id.*; *In re D'Ancicco*, 439 F.2d 1244, 58 CCPA 1057 (1971)." *In re Freeman*, 474 F.2d 1318, 1324 (CCPA 1973). Without evidence to the contrary, an applicant need only provide substantially improved results and state that the results were unexpected. *Soni*, 54 F.3d at 750; *In re Lee*, App No. 10/091,061, 2007 WL 176690 at *3 (BPAI June 19, 2007).

In *Soni*, the examiner rejected certain claims as obvious in view of a combination of references. The applicant directed the examiner to the data in the specification, and argued that the increase in tensile strength and the increase in peel strength rebutted the rejections. *Soni*, 54 F.3d at 747. On appeal to the Federal Circuit, it was argued that the Board "could have taken judicial notice of the fact that higher molecular weight polymers would have been expected to tolerate higher filler loadings without degradation in properties and that it could have taken notice of the fact that it is the polymer *per se* that primarily determines the mechanical properties of a filled polymer composition." *Id.* at 750. However, the Federal Circuit found this argument fatally flawed because the Board failed to support its position with facts or evidence. *Id.* at 750; see also *Lee*, 2007 WL 176690 at *3. In summary, the Federal Circuit held that "[m]ere improvement in properties does not always suffice to show unexpected results. In our view, however, when an applicant demonstrates *substantially* improved results, as Soni did here, and *states* that the results were *unexpected,* this should suffice to establish unexpected results *in the absence of* evidence to the contrary." *Soni*, 54 F.3d at 751.

Estetrol has a terminal elimination half-life of 28 hours, which is 168-336 times greater than estriol's terminal half-life. Thus, there is an actual difference and substantial improvement between estetrol and estriol.

One of ordinary skill in the art would have expected estetrol to be more comparable to estriol than estradiol given that (i) estetrol differs from estriol by only one hydroxyl group and from

estradiol by two hydroxyl groups and (ii) both estriol and estetrol are produced during pregnancy.[15] Thus, one of ordinary skill in the art would have expected estetrol to have a terminal elimination half-life similar to estradiol – on the order of a few minutes.[16] Unexpectedly, the Applicants discovered that estetrol's terminal elimination half-life was 28 hours.

The pharmacological activity of estetrol is associated with its unexpectedly long terminal elimination half-life. As discussed above, estetrol was known to be a very weak estrogen. So much so that it was dismissed by those of ordinary skill in the art as not being pharmacologically active.[17] Thus, it was unexpected to discover that estetrol, due to its unexpectedly long terminal elimination half-life, would be pharmacologically active.

Therefore, even assuming that a *prima facie* case of obviousness has been established, the unexpected results – that estetrol has an unexpectedly long terminal elimination half-life, and/or that estetrol is pharmacologically active – provide evidence that the recited invention is patentable over the cited references.

There was no reasonably expectation of successfully using estetrol in oral applications

Claims 31, 41 and 51 (which ultimately depend from claims 25, 35 and 45 respectively) further recite that the methods comprise ***oral*** administration. Prior to the disclosure of this invention, a person of ordinary skill in the art would not have expected estetrol to be pharmacologically active when orally administered.[18] Other human estrogens, notably estradiol, estriol and estrone, exhibit low oral bioavailability because they are largely metabolized into inactive metabolites during the so called "first pass" through the liver after oral administration.[19] Given that estetrol's estrogen receptor affinity was known to be considerably lower than that of estradiol and estriol, a person of ordinary skill in the art, being aware that known human estrogens are largely metabolized during the first pass, would have expected to find that estetrol likewise has low oral

[15] Declaration by Strauss at ¶ 17; and Declaration by Speroff at ¶ 17.

[16] Declaration by Strauss at ¶ 17; and Declaration by Speroff at ¶ 17.

[17] Declaration by Coelingh Bennink at Exhibit B.

[18] Declaration by Strauss at ¶ 7; and Declaration by Speroff at ¶ 7.

[19] Declaration by Strauss at ¶ 18; and Declaration by Speroff at ¶ 18.

bioavailability.[20] However, the Applicants unexpectedly discovered that estetrol has a very high oral bioavailability.[21]

In order to establish a *prima facie* case of obviousness, the Office Action must provide some reason why a person of ordinary skill in the art would consider estetrol to be pharmacologically active when orally administered in view of the fact that other natural estrogens where known to be metabolized into inactive metabolites. Since such a reason has not been provided, a *prima facie* case of obviousness has not been established.

It was unexpected that estetrol is bioavailable when administered orally

Moreover, it was unexpected that estetrol is pharmacologically active when orally administered.[22] According to the prior art, oral administration of estriol, for example, would not be an effective method of contraception because estriol would be metabolized very rapidly.[23] One of ordinary skill in the art would have expected estetrol to have similar oral bioavailability as estriol because both are natural estrogens differing by only one hydroxyl group.[24] Thus, it was unexpected to discover the high oral bioavailability of estetrol because, prior to the disclosure of the invention, there was no reason for a person of ordinary skill in the art to believe that estetrol was orally bioavailable.[25] Due to these unexpected results, the recited invention is patentable over the cited references.

Rejection of claims 29, 39 and 49

Claims 29, 39 and 49 have been rejected under 35 U.S.C. § 13 as purportedly being unpatentable over Elliesen in view of Holinka *et al.* in further view of Spicer *et al.* (U.S. Patent No. 5,340,584). Since these claims depend from claims 25, 35 and 45 respectively, they are patentable over the prior art for the same reasons.

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[20] Declaration by Strauss at ¶ 18; and Declaration by Speroff at ¶ 18.

[21] Declaration by Strauss at ¶ 18; and Declaration by Speroff at ¶ 18.

[22] Declaration by Strauss at ¶ 18; and Declaration by Speroff at ¶ 18.

[23] Declaration by Strauss at ¶ 18; and Declaration by Speroff at ¶ 18.

[24] Declaration by Strauss at ¶ 17; and Declaration by Speroff at ¶ 17.

[25] Declaration by Strauss at ¶ 7; and Declaration by Speroff at ¶ 7.

Conclusion

In view of the foregoing remarks, Applicants respectfully submit that all pending claims in the instant application are patentable over the cited references and are in condition for allowance. Accordingly, reconsideration and withdrawal of the asserted rejections, and allowance of claims 25-54 are respectfully requested. Should the Examiner have any questions or concerns, the Examiner is invited to contact Applicants' undersigned attorney by telephone at 412-471-8815.

Respectfully submitted,

THE WEBB LAW FIRM

By _____

William H. Logsdon
Registration No. 22,132
Attorney for Applicants
700 Koppers Building
436 Seventh Avenue
Pittsburgh, Pennsylvania 15219
Telephone: 412-471-8815
Facsimile: 412-471-4094
E-mail: webblaw@webblaw.com